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Diet in adolescence and the risk of breast cancer: results of the Netherlands Cohort Study

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Abstract

Objectives: In The Netherlands, part of the population experienced food restriction and severe famine during World War II. The purpose of this study was to study the effects of severe undernutrition during adolescence on the risk of breast cancer later in life.
Methods: We examined the hypothesis in the Netherlands Cohort Study on diet and cancer (NLCS), among 62,573 women aged 55–69 years. Baseline information on diet and other risk factors was collected with a questionnaire in 1986. Information was collected on residence in the Hunger winter (1944–1945) and War years (1940–1944) and fathers' employment status in 1932–1940 as indicators of exposure. After 6.3 years of follow-up, 1009 incident breast cases were available for analysis.
Results: In multivariate case-cohort analysis, residents of the western part of the country in 1944–1945 had an increased breast cancer risk (western city RR = 1.1, 95% CI: 0.9–1.4, western rural area RR = 1.5, 95% CI: 1.1–1.9). For the War years (1940–1944) we found no association between breast cancer risk and urban *vs*. rural residence. Women whose fathers were unemployed during the Depression years (1932–1940) had a non-significant decrease in breast cancer risk (RR = 0.9, 95% CI: 0.7–1.2). Exposure to energy restriction during the adolescent growth spurt or during the period between menarche and birth of the first child did not change the RRs substantially.
Conclusions: We found no clear evidence in this study for the hypothesis that energy restriction in adolescence leads to a decreased breast cancer risk.

Introduction

Among women in The Netherlands, breast cancer is the most frequent cancer accounting for almost one-third of all the cancer cases [1]. The hypothesis relating energy restriction to the risk of breast cancer is supported by longstanding results from rodent experiments documenting a reduced risk of breast cancer in animals on an energy-restricted dietary regimen [2]. Potential mechanisms for an effect of energy restriction early in life on decreased breast cancer risk can be summarized as follows: energy restriction in childhood and adolescence leads to a late age of menarche which leads to a decrease in breast cancer risk. Energy restriction in childhood and adolescence may also lead to a decrease in attained height. Attained height can act as an intermediate factor or as an independent risk factor for breast cancer. De Waard and Trichopoulos hypothesized that besides age at menarche and height, an energy-rich diet during childhood and adolescence could be an independent risk factor for breast cancer [3]. As a consequence of a high fat/high energy diet in childhood, breast development might be stimulated resulting in an increased susceptibility for initiating hits which lead to cells with more malignant potential.

Many studies have been conducted on the relationship between diet and breast cancer, but only a few concentrated on diet in adolescence. To investigate early dietary exposures in relation to later cancer risk, proxy measures are generally needed, as no individual data are available on diet early in life.

Hislop *et al.* conducted a case-control study to examine the relationship between childhood and current eating practices and the risk of breast cancer [4]. No elevated risks of breast cancer for the childhood consumption of foods with high fat content were found, except possibly for animal fat. Results of an ecological study in Norway showed that one or more environmental factors influenced the risk of breast cancer during World War II. The authors suggested that important factors to be considered were a decrease in fat and milk consumption, an increase in fish and fresh vegetables, and an increase in the physical activity level [5].

In The Netherlands, a substantial part of the population experienced a severe famine during World War II, the so-called Hunger winter (1944–1945), especially in the western part of the country. This unique setting provided the opportunity to study the effects of severe undernutrition during adolescence on the risk of breast cancer later in life [6–8]. In addition, a period of chronically impaired nutrition existed in The Netherlands during the earlier years of World War II (1940–1944) and the Depression in the 1930s. As a consequence of the poor availability of food products in the cities, nutritional differences developed between cities and rural areas during the war years [9, 10]. The available amount of calories was greater in the rural areas. Also, the ratio between the dietary nutrients was different for cities and rural areas. In the cities, carbohydrates contributed more to the total amount of energy (70 energy%) compared to the rural areas (65 energy%). The contribution of fat was also less in the cities compared to the rural areas (10 energy% *vs.* 15 energy%).

During the Economic Depression a large proportion of people were unemployed. Several surveys showed that in the food pattern of the unemployed families there was little variation and the energy intake was not at the same level as for the employed people [11–14]. The total amount of energy available for unemployed families compared to employed families was 3000 *vs.* 3400 calories [15]. The daily menu of the unemployed people was very sober, consisting of boiled potatoes and some fat. Also the bread meals underwent changes, no longer including cheese, meat and confectionary. The energy restriction in these three periods, Economic Depression, the War years and the Hunger winter is the subject of investigation in this study.

We examined the association between diet in adolescence and breast cancer risk in the Netherlands Cohort Study (NLCS) on diet and cancer. Women who were passing their pubertal years during the Economic Depression, the War and the Hunger winter were included in this prospective cohort study. There are biological reasons to believe that the period between the beginning of breast development at puberty and the first full term pregnancy is a particularly sensitive period in a woman's life regarding the development of breast cancer [16]. Russo *et al.* have proposed, on the basis of experiments in rats, that the full cellular differentiation of the mammary gland during a full-term pregnancy protects against the subsequent development of breast cancer. Therefore, the period between menarche and first full-term pregnancy might be critical for the initiation of breast carcinogenesis [17, 18]. In this study, we focused on the interaction with the age at which dietary restriction took place, with particular attention to those women who were exposed between menarche and delivery of their first child.

Materials and methods

The Netherlands Cohort Study started in September 1986 when 62 573 women 55–69 years were enrolled in the cohort. Baseline exposure data were collected by means of a self-administered questionnaire. The questionnaire referred to dietary habits and potential confounders such as reproductive history, smoking habits, education and family history of cancer. Also included were questions about the residences of the cohort members during their entire life, including the residence in the war years and the winter of 1944–1945 and the fathers' employment status during the Economic Depression. A detailed description of the cohort study design has been reported elsewhere [19]. After the baseline exposure measurement, a subcohort was randomly sampled from the cohort and followed up biennially for vital status information. Incident cancer cases occurring in the entire cohort have been identified by record linkage to cancer registries and a national pathology register (PALGA). The method of record linkage has been described previously [20].

The collected data from subcohort and breast cancer cases were key-entered twice by a research assistant who was blinded with respect to subcohort/case status in order to minimize observer bias in coding and interpretation of the data. The present analysis is restricted to cancer incidence in the 6.3-year follow-up from September 1986 to December 1992.

Completeness of cancer follow-up was estimated to exceed 96% [21]. After these 6.3 years of follow-up, 1009 breast cancer cases were available for analysis, after exclusion of prevalent cancer cases and cases with *in situ* breast carcinoma. Prevalent cancer cases other than skin cancer were also excluded from the subcohort, after which 1716 women remained. For data analysis the

case-cohort approach was used in which cases are derived from the entire cohort, while the person-years at risk are estimated from the subcohort.

Assessment of energy restriction

The exposure variables have to adequately represent the energy restriction of the women in the cohort for the Economic Depression years (1932–1940), the War years (1940–1944) and the Hunger winter (1944–1945). Individual food intake data of the women in these periods were not available; we, therefore, used proxy variables for the energy restriction in each of these periods. For the Economic Depression years (1932–1940), the occupation of the father was the best available proxy variable for energy restriction. Contemporary studies observed that having an unemployed father indicated that the family had less energy to consume and less variation in their food pattern compared to families with an employed father. The exposure variable for the Economic Depression years was dichotomous: women whose father had a job and women whose father had no job [11–15]. For the other two periods, the War period (1940–1944) and the Hunger winter (1944–1945), the city of residence during these periods was used to approximate the exposure for energy restriction. Living in a city in 1942 (midpoint year 1940–1944) with more than 40,000 inhabitants was considered as an indicator for energy restriction in the War period because of the documented nutritional differences between a city and a rural area [9, 10]. This exposure variable was dichotomous: women living in a city in 1942 or women living in a rural area in 1942.

With respect to the Hunger winter, three categories were defined, women who lived in a western city, women who lived in a western rural area and women who lived in a non-western part of The Netherlands. Living in a Western city in 1944–1945 was considered as an indicator for severe energy restriction. The definition of a famine city ($>40{,}000$ inhabitants) is based upon the definition of a famine city according to the study of Stein *et al*. [22].

In addition, the timing of exposure was of interest. Two periods can be distinguished in a woman's life in which energy restriction can have great influence on the development of the breast cells:

1. The 'adolescent growth spurt', in which menarche occurs [23] and in which enlargement of the breasts is starting. If less energy is available during the growth spurt the enlargement of the breasts will take place at a slower rate and the breasts may be less susceptible for initiation hits. The adolescent growth spurt in this study was defined as 2 years before the reported age at menarche until 1 year after the reported age at menarche.
2. The time span between menarche and birth of the first child, referred to as the sensitive period. During the first pregnancy the breast tissue differentiation is completed and until that moment the breast tissue is constantly sensitive to change and cell-dividing activities. If less energy is available for these cell-dividing activities the breast tissue may be less susceptible to carcinogenic exposures.

Women in the adolescent growth spurt or sensitive period in the three exposure periods were defined. Since the exposure periods are age-dependent and of varying duration, it was decided to restrict the relevant time span in the long exposure periods, 1932–1940 and 1940–1944, to the years in which the food situation was worst. For the Economic Depression period, we selected the years 1933–1934 because the literature regarding the Economic Depression showed a very poor food situation in the first years of the Economic Depression [11, 15, 24] and some improvement in the later years [12]. Thus, only women with the adolescent growth spurt or sensitive period in 1933–1934 were included in the subgroup. For the War period, we selected the years 1942–1943 because the food situation deteriorated progressively during the World War II years and the years 1942–1943 represent the worst years of the pre-famine period [10].

Data analysis

The distributions of the exposure variables were compared between the breast cancer cases and the female subcohort members. The associations between exposure variables and covariates were also studied in the subcohort. For the continuous covariates age, age at menarche, age at menopause, height, Quetelet index, alcohol intake and energy intake, mean values of these variables were compared between the exposure categories. Statistical significance of these associations was tested by *t*-tests and analysis of variance. Chi-square tests were conducted to test associations between exposure categories and the following categorical covariates: history of benign breast disease, familial breast cancer, parity, age at first birth and educational level. Age-adjusted analyses rate ratios (RR) were computed for the covariates for breast cancer. Covariates associated with breast cancer itself or with any of the exposure variables were considered as potential confounders. The effects of the risk factors were in the anticipated direction. A history of benign breast disease, a family history of breast cancer,

age at menopause, height, alcohol intake, age at first birth, parity, age at menarche, education and energy intake were considered as confounders. The same confounders for breast cancer had already been investigated in the NLCS-cohort in previous analyses concerning dietary fat and breast cancer risk [25].

Data were analyzed using the case-cohort approach [26, 27], age-adjusted RR's of breast cancer and 95% confidence intervals (95% CI) were calculated. Tests for trend were based on likelihood ratio tests provided by the GLIM statistical package. In multivariate analyses, adjustment for covariates was carried out. All analyses were carried out with GLIM [28]. To assess whether the effect of energy restriction on the risk of breast cancer was modified by the timing at which dietary restriction took place, rate ratios of breast cancer for energy restriction in each of the three periods were calculated within strata of the adolescent growth spurt and sensitive period, after adjustment for potential confounders (subgroup analyses). In these analyses, women were divided into subgroups depending on exposure to energy restriction before, during or after the adolescent growth spurt and sensitive period.

Results

In Table 1, the overall means of various continuous variables and distributions of various categorical variables in relation to the exposure categories among subcohort women are presented.

For the Hunger winter period, alcohol intake and energy intake during the year preceding the baseline measurement, age at first birth, parity and education were different between the three exposure categories. Women who lived in a western city in 1944–1945 had the highest level of alcohol intake in 1986 and the lowest level of energy intake in 1986 compared to women who lived in the western rural area or in some other parts of The Netherlands in the winter of 1944–1945. Furthermore, women who lived in a western city during the Hunger winter had the youngest age at menarche (mean, 13.6 years) and the lowest Quetelet index at baseline compared to women living in other parts of The Netherlands in 1944–1945. For women who were still at risk for their menarche at the start of the famine, the women living in a western city had the oldest age at menarche (mean, 15.8 years).

For the remaining war years (1940–1944), mean age at menopause and alcohol intake were significantly different between the exposure categories. Women who had lived in a city in 1942 had an early age at menopause (mean, 48.6 years) compared to women who had lived in a rural area in 1942 (mean, 49.2 years). Alcohol intake was significantly higher for women who had lived in a city in 1942. Women who had lived in a rural area in 1942 were taller (mean, 165.3 cm) compared to women who had lived in a city in 1942 (mean, 164.9 cm). Furthermore, the women who had lived in a city in 1942 had fewer children and a higher educational level compared to women living in a rural area in 1942.

For exposure during the Economic Depression, baseline age, age at menarche, age at menopause, height, alcohol intake and energy intake were significantly different between the two exposure categories. Women whose fathers did not have a job during the Economic Depression had a late age at menarche and an early age at menopause compared to women whose fathers had a job in this period. The women whose fathers had no job were also shorter and had a lower alcohol intake and energy intake in 1986 compared to women whose fathers had a job during the Economic Depression (Table 1). Women whose fathers were unemployed during the Economic Depression were considerably less educated compared to women whose fathers had a job during the Depression.

In Table 2, the results of the age-adjusted and multivariate analyses of exposure in the three periods and breast cancer risk are presented. The age-adjusted analyses show that there are differences in RRs for the three periods.

For the Hunger winter, a small increase in risk was seen for women who were then living in the western rural area, compared to the reference category of women living in non-western parts of The Netherlands (RR = 1.3, 95% CI: 1.0–1.6). Living in a western city during the Hunger winter period showed a small increase in risk (RR = 1.1, 95% CI: 0.9–1.3), which was not statistically significant. For exposure during the remaining War period, there was no difference in RR between women living in a rural area and women living in a city in 1942 (RR = 1.0, 95% CI: 0.9–1.2). With respect to the Economic Depression years, the analysis shows a small, nonsignificant decrease in risk for women whose fathers were unemployed (RR = 0.9, 95% CI: 0.7–1.2).

The associations between the risk of breast cancer and energy restriction were further evaluated in a multivariate model with adjustment for age, age at menopause, benign breast disease, maternal breast cancer, breast cancer in sister(s), age at first birth, parity, alcohol intake, energy intake and education. Age at menarche and height were not included in the model. The rate ratios were slightly changed compared to the age-adjusted analysis, as is shown in Table 2, but the multivariate adjusted RRs showed the same trend as in

Table 1. Means, standard deviations (s.d.) of selected continuous variables and distribution of selected categorical variables by food restriction exposure category in female subcohort members, Netherlands Cohort Study 1986–1992

	Exposure categories											
	1944–1945						1940–1944				1932–1940	
	Non-west		Western rural area		Western city		Rural area in 1942		City in 1942		Father with job	Father without job
Subcohort[a]	n = 900		n = 239		n = 454		n = 597		n = 624		n = 1419	n = 184
Cases[a]	n = 500		n = 167		n = 275		n = 350		n = 371		n = 856	n = 103
	mean	(s.d.)	mean	(s.d.)	mean	(s.d.)	mean	(s.d.)	mean	(s.d.)	mean (s.d.)	mean (s.d.)
Characteristics												
Age in 1986	61.4	(4.3)	61.3	(4.1)	61.7	(4.4)	61.5	(4.2)	61.6	(4.4)	61.4 (4.2)	62.1[b] (4.4)
Age at menarche	13.8	(1.7)	13.7	(1.8)	13.6	(1.9)	13.7	(1.7)	13.7	(1.8)	13.7 (1.7)	13.9[b] (2.1)
Age at menopause	48.8	(4.4)	48.8	(4.4)	48.7	(4.7)	49.2	(4.1)	48.6 [b]	(4.6)	48.9 (4.4)	48.0[b] (4.7)
Height (cm) in 1986	165.4	(6.3)	165.1	(6.1)	165.2	(5.9)	165.3	(6.1)	164.9	(6.1)	165.2 (6.2)	163.9[c] (6.7)
Weight (kg) in 1986	68.7	(10.4)	69.7	(10.6)	68.2	(10.0)	69.2	(10.3)	69.0	(10.3)	68.5 (10.1)	68.6 (11.0)
Quetelet Index (kg/m^2) in 1986	25.2	(3.6)	25.5	(3.6)	25.0	(3.4)	25.3	(3.5)	25.4	(3.5)	25.5 (3.5)	25.6 (3.8)
Alcohol (g/day) in 1986	5.3	(9.2)	5.3	(8.2)	6.9[d]	(10.8)	4.7	(8.0)	6.3[c]	(10.2)	6.0 (9.8)	4.4[b] (8.0)
Energy intake (kcal/day) in 1986	1692.1	(435.8)	1682.7	(433.8)	1623.4[e]	(388.3)	1683.0	(437.5)	1640.0	(398.0)	1676.4 (421.7)	1591.3[b] (430.6)
Parity (in %)												
nulliparous	17.6		18.3		18.8[a]		14.6		17.2[a]		18.2	13.8
1 child	7.0		6.1		11.4		7.5		9.4		8.4	8.8
2 children	21.6		24.3		24.0		20.5		23.7		22.2	22.2
⩾3 children	53.8		51.3		45.8		57.4		49.7		51.3	55.2
Age at first birth												
nulliparous	17.5		18.0		18.6[f]		14.6		17.0		18.0	13.8
17–19 yr	1.3		1.7		2.0		0.7		1.9		1.3	2.2
20–24 yr	19.1		22.7		25.1		21.0		22.8		19.6	33.7
25–29 yr	41.3		39.9		39.9		44.5		39.7		42.2	34.3
⩾30 yr	20.8		17.7		14.4		19.2		18.6		18.9	16.0
Level of education												
low	62.9		63.7		47.9[g]		72.0		49.3[g]		54.9	75.8[g]
medium	30.1		27.4		41.6		22.9		41.4		35.8	21.4
high	7.0		8.9		10.5		5.1		9.3		9.3	2.8

[a] due to missing values numbers may not add up till 1716 and 1009.
[b] $p < 0.05$ (t-test).
[c] $p < 0.005$ (t-test).
[d] $p < 0.001$ (ANOVA).
[e] $p < 0.01$ (ANOVA).
[f] $p < 0.005$ ((χ^2-test).
[g] $p < 0.001$ (χ^2-test).

Table 2. Age-adjusted relative rates and multivariate relative rates of breast cancer, according to food restriction exposure in three time periods, 1944–1945, 1940–1944 and 1932–1940, Netherlands Cohort Study 1986–1992

Exposure	Age-adjusted				Multivariate			
	Cases cohort	Person yrs. subcohort	RR[a]	95% CI	Cases cohort	Person yrs. subcohort	RR[b]	95% CI
1944–1945								
Non-West	500	5500	1.0[c]		418	4809	1.0[c]	
Western rural area	167	1468	1.3	1.0–1.6	144	1168	1.5	1.1–1.9
Western city	275	2768	1.1	0.9–1.3	239	2420	1.1	0.9–1.4
1940–1944								
Rural area in 1942	350	3639	1.0[c]		295	3084	1.0[c]	
City in 1942	371	3810	1.0	0.9–1.2	323	3411	1.0	0.8–1.2
1932–1940								
Father had a job	856	8677	1.0[c]		733	7552	1.0[c]	
Father had no job	103	1119	0.9	0.7–1.2	83	930	0.9	0.7–1.2

[a] Age in three categories; 55–59 yr, 60–64 yr, 65–69 yr.
[b] Relative rate after adjustment for: age, age at menopause, parity, age at first birth, maternal breast cancer, breast cancer in sister(s), benign breast disease, alcohol use, energy consumption, education, without age at menarche and height.
[c] Reference category.

the age-adjusted analyses. There was again no difference in breast cancer risk for women living in a city in 1942 compared to women living in a rural area in 1942. For women living in a western rural area during the Hunger winter 1944–1945, the analysis showed a significant increase in breast cancer risk compared to women who lived in non-western parts of The Netherlands (RR = 1.5, 95% CI: 1.1–1.9). Women whose fathers were unemployed during the Economic Depression years showed a decrease in breast cancer risk (RR = 0.9, 95% CI: 0.7–1.2) in multivariate analysis, although not significantly.

Age at menarche and height are two variables which might play a role in the possible biological explanations of our hypothesis. We conducted a multivariate analysis where additional correction was included for these two variables. This adjustment did not alter the RRs appreciably, but they were closer to 1 (see Table 3), suggesting that each of these two variables might act as intermediate variables. In further analyses, these two variables were not included in the multivariate model.

Additional comparisons with other reference categories were made in multivariate analyses. A comparison was made between the western cities and cities in other parts of The Netherlands and in a comparison between the western rural area and rural area in other parts of The Netherlands. By using different reference catego-

Table 3. Multivariate relative rates of breast cancer, according to food restriction exposure in three time periods, 1944–1945, 1940–1944 and 1932–1940 with age at menarche and height added to the model, Netherlands Cohort Study 1986–1992

Exposure	Model I[a]		Model II[b]		Model III[c]	
	RR	95% CI	RR	95% CI	RR	95% CI
1944–1945						
Non-west	1.0[d]		1.0[d]		1.0[d]	
Western rural area	1.4	1.1–1.8	1.4	1.1–1.8	1.3	1.0–1.7
Western city	1.1	0.9–1.3	1.1	0.9–1.3	1.1	0.9–1.4
1940–1944						
Rural area in 1942	1.0[d]		1.0[d]		1.0[d]	
City in 1942	1.0	0.8–1.2	1.0	0.8–1.2	1.0	0.8–1.2
1932–1940						
Father had a job	1.0[d]		1.0[d]		1.0[d]	
Father had no job	0.9	0.7–1.2	0.9	0.7–1.3	1.0	0.7–1.3

[a] Model I adjustment for: age, age at menopause, parity, age at first birth, maternal breast cancer, breast cancer in sister(s), benign breast disease, alcohol use, energy consumption, education and age at menarche.
[b] Model II adjustment for the variables named in model I without age at menarche but with height.
[c] Model III adjustment for the variables named in model I with height.
[d] Reference category.

ries, the RRs did not change substantially (data not shown).

We conducted several subgroup analyses to evaluate possible effects of the timing of energy restriction. As a consequence of the small number of cases in the subgroups, 'exposure before growth spurt in the Hunger winter' and 'exposure before sensitive period in the War years', some multivariate models did not converge. For these subgroups we only conducted an age-adjusted analysis. Exposure to energy restriction during the adolescent growth spurt (Table 4) shows for women living in a western city an increased risk (RR = 1.2, 95% CI: 0.8–2.0) compared to women living in non-western parts of The Netherlands. For women living in the western rural area, a significantly increased risk (RR = 1.8, 95% CI: 1.0–3.2) was seen compared to women living in non-western parts of The Netherlands during the Hunger winter, but the number of cases is very small and the 95% confidence interval is accordingly large. During the war years, there was no difference in risk between women living in a city during their adolescent growth spurt and women living in a rural area. The RR for the women whose fathers had no job in 1933–1934 and who were in their growth spurt at that time showed a decrease in breast cancer risk (RR = 0.8, 95% CI: 0.5–1.4) which was not statistically significant (Table 4). Again the number of cases is quite small.

The subgroups of women exposed after the growth spurt showed the same pattern as the group exposed during the growth spurt. But the subgroups of women exposed before the growth spurt showed a different pattern. A decrease in risk is seen for women living in a western city before their growth spurt (RR = 0.3, 95% CI: 0.03–2.0), however, the number of cases is very small. Also the women living in a city in 1942 before their growth spurt have a decreased risk (RR = 0.5, 95% CI: 0.2–1.3) (see Table 4).

Exposure during the sensitive period between menarche and birth of the first child showed the same pattern with breast cancer risk as exposure during adolescent growth spurt (see Table 5). The RR for the exposure category western city was nonsignificantly increased (RR = 1.1, 95% CI: 0.9–1.4). The RR for women living in the western rural area was again significantly elevated (RR = 1.4, 95% CI: 1.1–1.9) compared to the exposure category living in other parts of The Netherlands. There was no difference in breast cancer risk between women living in a city or rural area during the war years and in those who were passing their sensitive period in the war years. Also with respect to the Economic Depression years, no clear association was found between exposure during the sensitive period and breast cancer risk (RR = 0.9, 95% CI: 0.5–1.7).

The subgroups exposed before and after the sensitive period also showed the same pattern as the subgroup exposed during the sensitive period (Table 5). Only for the Hunger winter period there is a negative association (RR = 0.7, 95% CI: 0.3–1.6) for the exposure living in a western city in 1944–1945 before the sensitive period, although not significantly. With respect to the war years, living in a city in 1942 showed for the subgroup exposure before the sensitive period a decrease in RR (RR = 0.7, 95% CI: 0.3–1.7) but the number of cases is again very small. A small, non-significant, negative association with living in a city in 1942 (RR = 0.9, 95%

Table 4. Relative rate of breast cancer for women exposed to energy restriction before, during and after their adolescent growth spurt (2 yr < menarche < 1 yr) in the time-period 1944–1945, 1942–1943 and 1933–1934. Netherlands Cohort Study 1986–1992

Exposure	Before growth spurt				During growth spurt				After growth spurt			
	Cases	Person yrs	RR[a]	95% CI	Cases	Person yrs	RR[a]	95% CI	Cases	Person yrs	RR[a]	95% CI
1944–1945												
Non-west	8	100	1.0[b,c]		102	1308	1.0[b]		332	3348	1.0[b]	
Western rural area	3	18	1.4	0.2–9.5	32	297	1.8	1.0–3.2	112	858	1.3	1.0–1.8
Western city	2	100	0.3	0.0–2.0	60	604	1.2	0.8–2.0	182	1738	1.1	0.9–1.4
1942–1943												
Rural area in 1942	23	244	1.0[b]		81	964	1.0[b]		190	1823	1.0[b]	
City in 1942	33	335	0.5	0.2–1.3	74	970	1.0	0.7–1.5	215	2076	1.0	0.8–1.3
1933–1934												
Father had a job	463	5205	1.0[b]		226	1863	1.0[b]		40	407	1.0[b]	
Father had no job	54	571	1.1	0.7–1.6	24	270	0.8	0.5–1.4	5	75	0.7	0.2–3.1

[a] Relative rate after adjustment for: age, age at menopause, parity, age at first birth, maternal breast cancer, breast cancer in sister(s), benign breast disease, alcohol use, energy consumption, education.

[b] Reference category.

[c] Only age-adjusted.

Table 5. Relative rate of breast cancer for women exposed to energy restriction before, during and after their sensitive period (menarche-1st child) in the time-period 1944–1945, 1942–1943 and 1933–1934. Netherlands Cohort Study 1986–1992

Exposure	Before sensitive period				During sensitive period				After sensitive period			
	Cases	Person yrs	RR[a]	95% CI	Cases	Person yrs	RR[a]	95% CI	Cases	Person yrs	RR[a]	95% CI
1944–1945												
Non-west	32	410	1.0[b]		354	3951	1.0[b]		64	800	1.0[b]	
Western rural area	12	99	2.9	1.0–8.0	123	996	1.4	1.1–1.9	19	172	1.7	0.9–3.4
Western city	22	260	0.7	0.3–1.6	190	1895	1.1	0.9–1.4	48	498	1.1	0.6–1.8
1942–1943												
Rural area in 1942	18	165	1.0[b,c]		241	2282	1.0[b]		43	615	1.0[b]	
City in 1942	14	167	0.7	0.3–1.7	250	2528	1.0	0.8–1.2	62	718	0.9	0.5–1.6
1933–1934									no women who were after their sensitive period in 33–34			
Father had a job	585	6021	1.0[b]		144	1454	1.0[b]					
Father had no job	64	688	0.9	0.6–1.3	19	229	0.9	0.5–1.7				

[a] Relative rate after adjustment for: age, age at menopause, parity, age at first birth, maternal breast cancer, breast cancer in sister(s), benign breast disease, alcohol use, energy consumption, education.
[b] Reference category.
[c] Only age-adjusted.

CI: 0.5–1.6) was found for the subgroup exposure after the sensitive period.

Women whose fathers were unemployed during the Economic Depression years showed a negative association with exposure before the sensitive period, although not significant (RR = 0.9, 95% CI: 0.6–1.3). In 1933–1934, no woman in the cohort had already delivered her first child, thus, no women were exposed after their sensitive period at that time.

Possibly the food situation was not the most important factor (because for everybody the food situation deteriorated during the War) but being in the adolescent growth spurt during these years could be the most important factor. Therefore, we also conducted a multivariate analysis for the War years in which exposure was defined as a combination of the residence in 1942 and being in the adolescent growth spurt in 1942. The subgroup of women who lived in a city in 1942 during their adolescent growth spurt showed a borderline significant decrease in breast cancer risk (RR = 0.7, 95% CI: 0.5–1.0) compared to all women who were before or after their adolescent growth spurt irrespective of their residence in 1942 (data not shown).

Discussion

This prospective cohort study found no clear evidence that energy restriction during adolescence decreased the risk of breast cancer, even after controlling for potential confounders. The results showed an increased breast cancer risk for those living in the presumably food-restricted regions such as western cities (RR = 1.1) as well as for those living in a western rural area in 1944–1945 (RR = 1.5), compared to residents living in the north and south of the country, who served as controls with almost no exposure to energy restriction. With respect to the war period (1940–1944), no differences in breast cancer risk were found for women who lived in a city (food restricted area) in 1942 *vs.* women who lived in a rural area. Having an unemployed father during the Economic Depression years 1932–1940 was associated with a small, but not significant, decrease in breast cancer risk (RR = 0.9).

Several alternative explanations for the results will be discussed. The potential for selection bias in the NLCS is low considering the high completeness of cancer follow-up. Also, there were no reasons to assume that residual confounding was still present, because all major risk factors for breast cancer were measured and controlled for in multivariate analyses.

Differential recall of major events such as age at first birth, parity, age at menarche and residence during the Hunger winter seems unlikely. A factor that could have influenced the results is misclassification of food restriction exposure. Three proxy measures of energy restriction were used in this study: the fathers' employment status of the women during the Economic Depression years, residence during the World War II (1940–1944), and residence during the Hunger winter (1944–1945). Whereas surveys showed that energy intake was associated with fathers' employment status in 1932–1940 [11, 13, 14], that the food supply in the cities deteriorated much faster than in the rural area during 1940–1944 [9,10] and that

starvation in the west in 1944–1945 was mostly confined to western cities [6–9], we are aware that these ecological measures are only a proxy measure of individual exposures. Other studies used the same proxy measure for energy restriction in the Hunger winter. These studies found a relationship, between living in a western city and perinatal mortality of the newborn, lower birth weight and delay in the onset of menarche. These studies had a more complete exposition available in their study population compared to the population of the NLCS-cohort. Most of the women in the NLCS-cohort had already passed their menarche. The severe energy restriction during the hunger winter could, therefore, no longer affect the age of menarche of these women.

Also long-term effects have been reported on the birth weight of offspring of women who were themselves conceived during the famine period. These results indicate that the residence in 1944–1945 is a good predictor for energy restriction and is likely to be a valid measure [22, 29–34]. In our study, we asked only the female subcohort members during follow-up, if they really had experienced hunger during the winter of 1944–1945. Our results showed that 75% of the women living in a western city reported that they experienced hunger during the winter of 1944–1945 of whom 35% experienced severe hunger. Of the women who reported severe hunger during the Hunger winter, 80% lived in a western city during this winter. These results also indicated that the proxy measure for energy restriction in the Hunger winter is reasonably adequate.

In our study the period of severe energy restriction was relatively short in the Hunger winter (only 7 months of severe deprivation, *i.e.*, less than 40% of normal energy-intake) [6]. The short duration of energy restriction could be a possible explanation for not finding an effect on breast cancer risk. Nevertheless, the famine had an effect on reproductive factors of women who gave birth during and after the Hunger winter and were exposed to the famine [31–34]. A delay in the birth of the first child is seen in the NLCS, although the number of births is very small and this effect is seen in the whole country.

With respect to the War years (1940–1944), no association was found between living in a city and breast cancer risk. During World War II, the food situation leveled off for everybody, for people living in the city as well as for people living in rural areas [35]. Therefore, the contrast in energy intake between the exposure categories was probably not sufficient to detect an effect of energy restriction [5]. In addition, we defined exposure as a combination of residence in 1942 and being in the adolescent growth spurt. For women who lived in a city in 1942 and were in their adolescent growth spurt, a borderline significant decrease in breast cancer risk was seen (RR = 0.7). This definition of exposure suggests that energy restriction has more impact on women being in the adolescent growth spurt than on women only living in a city in 1942. Possibly, the adolescent growth spurt is a more important factor than residence in 1942.

Another possible explanation of our findings could be the opposite effects of energy restriction on selected breast cancer risk factors. Energy restriction may delay age of menarche, which may lead to a decrease in breast cancer risk. In our study, a delay in age of menarche is seen for women who were still at risk for their menarche at the beginning of the Hunger winter (mean age of menarche, 15-years). This effect was seen in the whole country and not only for the Western region. However, due to energy restriction and social circumstances during the Hunger winter, a delay in the birth of the first child could have also occured, which may have led to an increase in breast cancer risk. These opposite effects of energy restriction early in life could have resulted in no overall effect on breast cancer risk later in life.

Height is a risk factor for breast cancer in the NLCS-cohort [36]. Energy restriction early in life may negatively affect attained height, which might itself lead to a reduction in breast cancer risk [37–40]. Our data show that the variable adult height is associated with the exposure in the Economic Depression years. Women whose fathers were unemployed during the Economic Depression are significantly shorter than women whose fathers had a job during this period (Table 1). Therefore, the longer period of relatively minor food deprivation during the Economic Depression years could have had an effect on adult height and, consequently, on breast cancer risk. Adult height was not associated with exposure in the War years and the Hunger winter.

The cohort could have been too old at the time of exposure. During exposure in the Hunger winter no women were under 13 years of age. The influence of energy restriction might play a role earlier in life than around the age of menarche. The results of the subgroup analyses point in this direction. Subgroups, in which exposure before growth spurt and sensitive period was analyzed, showed a decrease in breast cancer risk for women living in a western city in 1944–1945 and for those living in a city in 1942 and having an unemployed father during the Economic Depression years (only for exposure before the sensitive period), although the number of women in the subgroups was very small. These analyses should be repeated when follow-up data is available for later years with a larger number of cases.

Another explanation for the elevated breast cancer risk in the western rural area could be the choice of the reference category. For various reasons, the western part

of The Netherlands may not be directly comparable to the other parts of The Netherlands. Specifically, because of historical migration patterns, there may be region-specific breast cancer risks. In the NLCS, the western rural area did not differ from the western cities or other parts of The Netherlands in breast cancer risk factors (see Tables 1 and 2). However, whereas the western Netherlands was exposed to severe food and fuel shortages during the winter of 1944–1945, the overall reproductive casualty rates (stillbirths plus infant mortality) were no worse in the west, and for most of the time, considerably lower than in the north and south of the country [7, 8]. As an explanation for this paradox, selective migration of the healthiest and best fed women towards the west has been postulated [41]. It is possible that this has led to regional baseline differences in breast cancer risk.

We made an additional comparison with different reference categories for the Hunger winter period 1944–1945. When the multivariate analysis was limited to the western region, the RR for the women who lived in a western city is decreased (RR = 0.7), compared to women who lived in the western rural area.

In conclusion, we found no strong support for the hypothesis that energy restriction in the defined periods of adolescence leads to a decrease in breast cancer risk in adults living in The Netherlands. In future studies, the effects on breast cancer risk should be explored among populations who experienced energy restriction for a longer period of time, especially before menarche.

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